EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 1 Cases*	

EXPERT REPORT OF TERI LONGACRE, MD

I. BACKGROUND AND QUALIFICATIONS

I am a board certified diagnostic surgical pathologist at Stanford Medicine with subspecialty expertise in gynecologic pathology. I received undergraduate degrees in the liberal arts (B.A.) at St. John's College in Santa Fe, New Mexico and in biology (B.S.) at the University of New Mexico in Albuquerque, New Mexico. I subsequently received my M.D. in 1985, also at University of New Mexico. I trained in Anatomic and Clinical Pathology at the University of New Mexico, followed by a surgical pathology fellowship at Stanford University. Thereafter I took a position as Assistant Professor at Stanford University and rose through the ranks of the professoriate at Stanford University, where I currently hold a position as Professor of Pathology. I am the Director of Gynecologic Pathology and Director of the ACGME-approved fellowship in Gynecologic Pathology, a program which I founded in 2007. In addition, I am the Director of Gastrointestinal Pathology and Director of the ACGME-approved fellowship in Gastrointestinal Pathology, a program which I also founded in 2013. I am the Director of the Stanford Hospital Tissue Committee and a member of the Stanford Care Improvement Committee which oversees the quality of care in the hospital. In addition to many other extramural committee appointments, I am the President Elect of the Association of Directors of Anatomic and Surgical Pathology, in part due to my prior work as a Director of Surgical Pathology at Stanford.

I have internationally recognized expertise in nonneoplastic and neoplastic gynecologic pathology and have published extensively in the peer-reviewed medical literature on gynecologic pathology. I provide continuing medical educational lectures for practicing pathologists regionally, nationally and internationally in gynecologic pathology and am author of numerous review articles, book chapters and a textbook in gynecologic pathology. I also provide annual medical student, resident, and fellow lectures at Stanford Medicine in areas of nonneoplastic and neoplastic gynecologic pathology and examine gynecologic pathology specimens, including mesh explant specimens when submitted to pathology, on a routine basis. Because of my expertise in gynecologic pathology, I was invited to become a member of the American Board of Pathology test committee in order to provide gynecologic pathology questions for the certification exam for pathology residents as well as the maintenance of certification exam for practicing pathologists. I am a member of a number of pathology societies and editorial boards, a list of which is provided in the attached curriculum vitae.

My clinical diagnostic activities chiefly include examination of surgical gynecologic and gastrointestinal specimens, including small biopsies and large organ resections. My annual case volume amounts to 5,000 to 7,500 cases. In my role as a diagnostic surgical pathologist, I routinely provide clinical and pathologic consultations to physicians at Stanford Medicine; this entails macroscopic (gross) and microscopic review of specimens, review of relevant clinical information, and rendering diagnoses on the basis of this review. As I am board certified in clinical pathology, I am well equipped to integrate findings in the areas of chemistry, hematology, microbiology, immunology, molecular pathology and other special laboratory studies as they relate to my practice of gynecologic pathology. I am a regular participant in the Stanford Gynecologic Oncology Interdisciplinary Tumor Board as well as several Gastrointestinal Tumor Boards. In addition to the clinical work I provide for Stanford patients, I also receive requests for my consultative opinion from both pathologists and treating physicians regionally, nationally, and internationally.

My opinions that follow, which apply to Ethicon's TVT, TVT-O, TVT-Exact, TVT-Abbrevo, Prolift, and Prosima, are held to a reasonable degree of medical and scientific certainty. Attached to this report are my curriculum vitae (Ex. A), which sets out my education and training in detail and lists my peer-reviewed publications, committee appointments, invited and active grant funding; a list of the materials I reviewed for these cases and materials/exhibits which I will use to support my opinions (Ex. B.); and a list of cases where I have testified in the last four years (Ex. C). I expect to review the deposition transcripts of certain of plaintiffs' experts in this case and may further develop my opinions after having done so.

II. TVT MIDURETHRAL SLING MESH IMPLANT

Foreign material, however inert, when implanted into human tissue typically invokes an inflammatory response in the initial phase which can be associated with acute inflammation, but generally evolves into a more chronic tissue response, with associated

lymphocytes, mast cells, and macrophages. The macrophages may form multinucleated foreign body type giant cells in response to the foreign material and often remain closely associated to the foreign material. The response to TVT mesh is similar to this general response and is often also associated with a thin zone of fibrosis. Following the initial early tissue reaction, the acute inflammatory response typically disappears and the only remaining inflammatory cells are chronic inflammatory cells, consisting of lymphocytes, plasma cells, mast cells, macrophages, and occasionally, eosinophils. The macrophages generally arise from tissue monocytes. The term "chronic inflammation" denotes the shift in the type of inflammatory cells and is not necessarily meant to denote severity of inflammation.

The surrounding zone of fibrosis and response to mesh implantation allows integration of the tissue into the mesh. Numerous controlled studies, clinical trials, and animal studies support the concept that the pore size of the mesh (75 µm) allows entry of cells (neutrophils, lymphocytes, macrophages, fibroblasts, red blood cells, and foreign body multinucleated giant cells) with microcapillary formation to accomplish the integration process. The integration process facilitates vascularization of the tissue adjacent to the mesh material, allows nutrients to replenish the tissue, and prevents excessive mobility of the mesh material while retaining sufficient flexibility of the adjacent surrounding normal fibroconnective tissue. In summary, the TVT mesh initially evokes a mild acute inflammatory response, which subsides into minimal to mild chronic inflammation often with associated foreign body type macrophage response, and localized fibrosis, which allows integration of the mesh into the surrounding fibroconnective tissue. This is consistent with my experience with the mesh explants that I have examined at Stanford, including those removed for reasons unrelated to any symptoms relating to the mesh.

Factors that may impact integration of the mesh are similar to those factors that impact wound healing in general (diabetes, smoking, poor nutrition, age). The presence of inflammation in association with the mesh material represents a normal host response. Inflammation occurs with any surgical procedure even in the absence of mesh or other foreign material. Inflammation may also occur in absence of surgery. Chronic inflammation is considered a normal healing response and is a normal physiologic reaction to any implanted device. There exists a normal complement of chronic inflammatory type cells in normal mucosal and submucosal tissue and it is often these cells that are recruited to form the chronic inflammatory response in response to implantation of foreign material. Tissue reactions to injury may vary from patient to patient dependent on a variety of factors. For example, some people develop more fibrosis or form scar tissue more readily than others. Factors influencing the scope and/or severity of tissue reaction include the degree of tissue injury as well as an individual patient's unique response to the injury (genetics, smoking, diabetes, etc.).

Polypropylene material has been used in most surgical specialties for over five decades, in millions of patients in the US. The TVT sling, with its macroporous, monofilament,

polypropylene mesh, has demonstrated long-term durability, safety, and efficacy up to 17 years. The 17-year data demonstrates a high cure rate and a very low complication rate; this low complication rate includes pain, dyspareunia, and mesh exposure, each of which occur in less than 5% of patients. Numerous scientific papers in respected peer-reviewed medical journals in the U.S. and the world support the use of mesh material as a treatment for stress urinary incontinence. Multiple randomized, controlled trials comparing types of midurethral sling procedures, and other established non-mesh procedures, have consistently demonstrated its clinical effectiveness and patient satisfaction.

Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of stress urinary incontinence and represent the current state of the art treatment of this condition. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated stress urinary incontinence. There have been over 100 surgical procedures developed for the management of stress urinary incontinence and there is scientific evidence that the midurethral slings are associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to other historic procedures. Organizations of gynecologic surgeons continue to support the use of polypropylene mid-urethral slings for the treatment of stress urinary incontinence.

The FDA has stated that polypropylene is safe and effective in the treatment of stress urinary incontinence. In 2013, the FDA website stated: "The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one year."

There is no correlation between the degree of fibrosis and inflammation and the presence of pain and/or mesh exposure. In fact, midurethral sling explants removed due to voiding dysfunction demonstrate more inflammation than those that are removed for pain and/or mesh exposure. Moreover, the degree of fibrosis and foreign body giant cell reaction is similar whether the mesh is removed for pain or voiding dysfunction. The presence of a foreign body reaction is a normal tissue response to the mesh material and has been observed in the vaginal tissue in all patients who have undergone mesh placement. Based on my accumulated experience of mesh explant pathology specimens at Stanford Medicine, chronic inflammation, often with associated foreign body response in mesh explant material is an expected finding in mesh explants, including those that are removed for reasons other than pain or dyspareunia. There are no compelling data that document significant histologic findings in mesh explants from patients with symptoms (pain, exposure, voiding dysfunction, etc.) versus mesh explants from patients who are entirely asymptomatic. Moreover, the cumulative literature data on mesh explants does not enable a pathologist to reliably and reproducibly correlate the pathology findings in mesh explant material to any specific symptom. Although there are several studies that attempt to compare the histology findings in mesh material removed from symptomatic and asymptomatic patients, valid comparisons cannot be drawn and clinical pathologic correlations cannot be made on the basis of the current data. In particular, the presence of fibrous tissue is normal, expected

and seen in all patients regardless of the presence of pain and/or exposure. There is no reliable scientific basis to conclude fibrosis of mesh leads to complications, particularly pain. One recent study found no difference in fibrosis between patients with pain and those without pain.

Mesh integration into the surrounding vaginal tissue is key to adequate mesh function. Following mesh implantation, a fibrin matrix is established as a scaffold for further fibroconnective tissue collagen deposition, ingrowth of blood vessels. The new blood vessels and capillaries supply nutrients for the fibroconnective tissue, including the surrounding nerves and permit fibroblasts to synthesize collagen. The initial loose granulation tissue that is formed is gradually replaced by firmer fibrous tissue with contractile properties that serves as a pliable, but strong support structure for the implanted mesh. Wound contraction occurs naturally as a result of this process, aiming to minimize the volume of maturing scar and reapproximate the existing tissue to its normal pre-implant state. The pores in the mesh allow this process to proceed more effectively as they permit incorporation of the fibroblasts into the mesh material, resulting in a knitted or more integrated mesh which is anchored into the fibroconnective tissue. This provides flexibility as well as stability. The degree of mesh contraction is minimal and unlikely to be clinically significant. In fact, in vivo ultrasound assessment of midurethral slings suggests that shrinkage and compromise of the implanted mesh does not occur in the physiologic state. Apparent contraction or shrinkage of the mesh once it is removed from the body is due to normal retraction that occurs with any tensile tissue; tissue dehydration (if not properly fixed), tissue fixation and processing also contribute to contraction of the mesh following removal and this is not something that can be reliably detected on routine or polarized light microscopy.

Several studies, including some by Ethicon, have suggested there may be degradation of the mesh following implantation. These data, when taken in aggregate are not compelling arguments at this point in time. First, it is not clear that degradation occurs to any extent in vivo. Second, if it does, the clinical data do not provide any support that such degradation translates into any clinically significant effect on mesh function/dysfunction, pain, infection, erosion, or other potential side effects of mesh implantation. The degradation data is largely based on ex vivo studies and the use of histology using routine and polarizing methods. The histologic appearance and apparent change in the staining properties of the mesh material is not an adequate or scientifically accepted method to assess degradation of materials. Plaintiffs' pathology expert, as a pathologist, has not presented scientifically reliable evidence sufficient to assess the molecular structure of substances.

Plaintiffs' pathology expert asserts mesh migration and mesh deformation can be identified by histopathologic examination of mesh explant tissue. This issue is best left to the surgeon – not pathologists after the mesh has been removed. Mesh material, as well as normal human tissue can change shape, fold, and "curl" following removal from the body, but this cannot be reliably shown to reflect an altered shape or "curling" while it is in the body. In fact, it is far more likely

to result from the removal procedure when it is being separated from the surrounding tissue with which it is integrated.

The presence of nerve twigs is normal and expected in this region and is desired in the integrated mesh material as it reflects full integration. The purpose of innervation in the vaginal area is multifold, but it is chiefly autonomic (i.e., not voluntary motor or sensory in the sense of pain sensation), and so the presence of nerves or nerve twigs in and around the mesh material does not necessarily (and in fact is unlikely to) reflect the presence of increased pain sensation.

There is a well-documented risk of infection following any surgical procedure and/or implantation of foreign material. The proliferation and subsequent maintenance of small capillaries – which is part of the initial inflammatory response – is important in the prevention of infection as this provides a source for supply of cells and nutrients including oxygen to the mesh, as well as removal of cellular debris. The macroporous, monofilament properties of TVT mesh facilitate the body in clearing bacteria and other infectious agents in order to minimize this risk of infection. The rate of infection with TVT is low.

There are a variety of theories to explain pain and there are medical doctors who have scientific expertise in this area and who are specifically trained to treat patients with pain. This area of medicine is not part of routine anatomic or clinical pathology and generally lies outside the expertise of the anatomic surgical pathologist. In absence of a reliable evidence base tying histologic changes to complications, it is disingenuous and misleading to render definitive statements about innervation of mesh material and resultant pain with respect to the pathologic examination of mesh explant material. Moreover, although anatomic pathologists do examine tissue containing nerves and nerve twigs during routine practice, the assessment of subtle neural damage, neural injury, abnormal neural growth, and neurovascular bundles cannot typically be correlated to a patient's symptoms.

Summary Opinion

Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of stress urinary incontinence and represent the current state of the art treatment of this condition. The FDA has concluded that polypropylene mesh is safe and effective in the treatment of stress urinary incontinence. As with any surgical procedure that involves implantation of foreign material into the human body, there is a small (significantly less than 5% overall) well known and well documented complication rate that has been associated with polypropylene mesh midurethral slings. This complication rate is less than that which has been associated with other surgical sling procedures that do not utilize mesh. Moreover, the surgical recovery rate and efficacy is better for polypropylene mesh midurethral slings than for the historical surgical procedures that were used prior to the development of the polypropylene sling.

As with any foreign material, however inert, polypropylene mesh acts as a foreign object and the body mounts an active foreign body reaction to the mesh at the time of implantation. This is a normal response and stabilizes once the mesh integration has occurred. Residual evidence of the reaction is present at the time of mesh explantation and this can be seen on histologic evaluation of the mesh. The degree of foreign body reaction and fibrosis in response to the mesh is typically minimal (mild to focally moderate at most) and is similar to that seen in the tissue in association with removal of any foreign material and is seen in all patients, whether that material is functional or nonfunctional or whether the patient is experiencing pain or no pain. In other words, the degree of inflammation and/or fibrosis cannot be used to predict or correlate symptoms in any individual patient.

The mesh itself, as a foreign object, and the body reaction to the mesh do not significantly damage the tissues in this anatomical location. For good functioning, it is desirable that the mesh be integrated into the adjacent tissue. After implantation, the innervation and vascular supply are restored through and/or around the mesh to facilitate integration. The integration process involves formation of a thin fibrous scar and a foreign body reaction, which when stabilized over the course of several weeks, allows the mesh to conform to the normal structures at that site and provide needed strength to prevent incontinence. The ingrowth of vessels and nerve innervation allows the tissue adjacent to the mesh to remain viable and functional.

While scar formation does occur, it is typically minimal and does not lead to deformation of the mesh.

The presence of nerve fibers and twigs in the area near and adjacent to the mesh reflects healthy tissue and healthy mesh integration. Since most nerve fibers in this area are autonomic, (and do not carry pain stimuli) their presence in the histologic sections of explanted mesh does not imply increased risk for pain; nor do they correlate with actual increased pain sensation. I have not encountered traumatic neuromas (which may be associated with pain) in mesh explants. Occasionally, mesh explants may contain foci of neural ganglia**.** This is not uncommon in tissue that is surgically excised from this site for other reasons – as this is a site that contains nerve ganglia – and is not necessarily a reflection of impaired nerve functioning. Neural ganglia in peripheral tissues are associated with the autonomic nervous system.

Mesh erosion with TVT slings is a rare complication – this is a known complication. Mesh erosion is likely due to a multitude of factors including infection, inherent poor vascular supply, and poor or impaired wound healing, etc.

The degree of inflammation is minimal (mild to focally moderate at most) in mesh slings once integration is complete and this degree of inflammation has no known correlation with the perception of pain. Tissue edema is also minimal once integration has occurred.

Mesh migration, folding and curling may rarely occur but this is documented by the surgeon and cannot be identified on the basis of examination of removed mesh – either on macroscopic or microscopic evaluation.

Conclusions about the presence of folding or curling of explanted mesh are based on an erroneous assumption that the configuration of the tissue and mesh removed from the supporting connective tissue in a patient accurately reflects the configuration of the tissue and mesh while in the body. It is well known that tissue retracts, contracts, folds and curls to varying degrees immediately following surgical removal as a result of loss of the surrounding supporting connective tissue that is essentially holding it in place. This retraction and contraction also applies to tissue that contains polypropylene mesh. The resulting configuration of the mesh material once it is removed from a patient depends on the manner in which it is removed, the amount that is removed, the integrity of the mesh material that is removed (i.e., partial mesh versus entire width), and the treatment following removal. If the mesh material is not placed in fixative immediately following removal and pinned out on cork board, the attached tissue may desiccate, causing artefactual distortion of the tissue as well as the mesh. The sectioning of the mesh explant – including that by scalpel as well as by microtome may further art factually distort the tissue and mesh material. The process of embedding the tissue and mesh into paraffin may create a plane of sectioning that is distorted and does not reflect the plane of the mesh when positioned in the body.

The pathologic examination of mesh explant material provides important information: (1) documentation that mesh was removed; (2) information as to whether or not there is concomitant infection and/or abscess that requires further treatment; and (3) documentation that other vital tissue was not removed (i.e, ureter, bladder wall, etc). The histopathologic evaluation of mesh explant material is not capable of identifying causes of pain, dyspareunia, or incontinence. In addition, the histopathologic examination of explanted mesh is not the method to be used to determine mesh cracking, degradation, twisting, or curling.

III. PELVIC ORGAN PROLAPSE MESH IMPLANTS

Although the quality of evidence is low to moderate (largely due to poor reporting and absence of large scale follow up studies), vaginal pelvic organ prolapse mesh is associated with slightly lower rates of awareness of prolapse, reoperation for prolapse, and recurrent prolapse on

examination, but slightly higher rate for reoperation due to prolapse, urinary incontinence, and mesh exposure when compared to native tissue repair. Mesh exposure appears to be the most common complication with pelvic organ prolapse mesh and this rate is higher than that seen with mid-urethral slings. Pelvic pain and dyspareunia are common complaints after prolapse surgery whether by transvaginal mesh repair for apical prolapse, laparoscopic sacrocolpopexy, or abdominal sacrocolpopexy.

Ethicon's pelvic organ prolapse mesh (Prolift and Prosima) contains fibers that are thinner (80-90 microns versus 120-150 microns) and contains a larger pore size (2.4 x 1.7 mm versus 1379 microns) when compared to the mesh used in mid-urethral slings. However, the host response to the implantation of Ethicon's pelvic organ prolapse mesh (Prolift and Prosima) is identical to that which occurs with Ethicon's TVT slings. In brief, the implanted mesh evokes an inflammatory response in the initial phase which can be associated with acute inflammation, but generally evolves into a more chronic tissue response, with associated lymphocytes, mast cells, and macrophages. The macrophages often form multinucleated foreign body type giant cells in response to the foreign material and often remain closely associated to the foreign material. Following the initial early tissue reaction, the acute inflammatory response typically disappears and the only remaining inflammatory cells are chronic inflammatory cells, consisting of lymphocytes, plasma cells, mast cells, macrophages (including foreign body type multinucleated giant cells), and occasionally, eosinophils.

Since the host response is similar for both mesh materials, the histologically observed inflammatory response, including giant cells and fibrous tissue ingrowth cannot be attributed to the observed higher complication rates associated with the pelvic organ prolapse mesh. Moreover, the issues identified in my report with respect to the purported degradation that occurs in vivo with mid-urethral sling mesh material are equally applicable to the pelvic organ prolapse mesh material.

IV. RESPONSE TO PLAINTIFF'S EXPERT OPINIONS AND PHOTOGRAPHS

The pathology photographs that are contained in the plaintiffs' experts' (Dr. Iakovlev) general report are limited by (1) absence of information about how immunostains were performed (antibody, titer, positive/negative controls, CLIA laboratory) (2) focus on specific areas without a low magnification image to identify site that is shown at higher magnification, (3) the use of yellow coloring in areas of prior mesh material and other apparent color alteration of images, (4) absence of paired H&E and immunohistochemical stained slides, (5) and incorrect magnifications. In addition, he repeatedly identifies "normal tissue" as fat or adipose tissue without recognizing that other normal tissues are present in many of the figures – including normal tissue in areas he identifies as "scar" or "edema". Specific comments are as follows:

Dr. Iakovlev's observations concerning polypropylene degradation in vivo are incomplete and not compelling. Microscopic examination of explanted mesh with the use of histochemical dyes and polarizing microscopy is not a scientifically appropriate method to study degradation or deformation of foreign material. These evaluation procedures are designed to study human tissue – in particular the chemical dyes that are used are designed to highlight acidic nucleic acids and basic proteins -and are based on the formation of chemical bonds. The use of immunohistochemistry (S100, myeloperoxidase, etc.) is designed to identify cell types and is not utilized for evaluation of extracellular substances. Extracellular matrix may take on artefactual staining with a variety of immunohistochemical stains, particularly along tissue edges (so-called edge effect) and along the edges of foreign materials and such reactivity cannot be interpreted as evidence for the presence of a specific reaction.

The surgical process for the removal of integrated mesh from a patient often requires pulling of the material with blunt and sharp dissection, which may cause distortion in the macroscopic and microscopic appearance of the mesh material. Additional distortion of the material occurs as a result of electrocauterization to prevent bleeding during the surgical removal. During the subsequent processing of mesh explant material for preparation of histologic slides, the mesh is exposed to formalin, varying thermal conditions, and solvents, including xylene. This processing is necessary in order to cross-link cell proteins for tissue stabilization and sectioning. However, it also alters the histologic staining and refractile properties of the mesh material in a similar manner to that which has been attributed to in vivo degradation.

Figure Set 1. The photographs show the presence of chronic inflammation and foreign body giant cell reaction around mesh spaces and fibers. The infiltrate is mild to focally moderate and limited to the immediate vicinity of the fibers. The "scar" area labeled in Figure 1b is normal tissue. The chronic inflammation, foreign body response, and scar areas that are depicted are limited to the mesh spaces and fibers, and are a normal and expected host response.

Figure Set 2. These photographs depict similar findings to those in Figure 1 and are normal and expected host responses. There is no "scar encapsulation". The mesh provides a scaffold for the deposition of collagen to provide strength and support to the surrounding connective tissue. Much of the tissue labeled as "scar" in 2b - 2e is normal fibroconnective tissue that contains small vessels. Normal pelvic floor tissue consists of fibrous tissue as well as adipose tissue. In 2g, the smooth muscle actin stain that has been performed to show the presence of smooth muscle depicts muscle and what appear to be small blood vessels in the area of "bridging fibrosis". This indicates normal tissue and not scar. The term "bridging fibrosis" is used in the area of liver pathology and is not a generally accepted term in the area of soft tissue fibrosis or scar formation.

Figure Set 3. These photographs show nerves and ganglia adjacent to mesh spaces and fibers. The nerves do not exhibit degeneration. No traumatic neuroma is present. A traumatic neuroma consists of nerves with axonal sprouting and surrounding perineural fibrosis. The photographs depicted in this set do not demonstrate axonal sprouting or significant fibrosis. Although several of the nerves are curved and thus appear to be distorted, this is likely due to manipulation of the mesh during removal or during histologic processing and sectioning (i.e., artifact). The foreign body response is limited around the mesh fibers and spaces and there is no inflammatory infiltrate in proximity to the nerves. The presence of nerves that appear histologically normal in between areas where mesh fibers are encountered indicate the restoration of normal connective tissue, which is the expected and desired effect. S100 immunostaining is a useful immunohistochemical stain to identify neural tissue, but discontinuity of staining is common and does not reflect neural injury. It is likely that the incision during placement of the mesh cuts through nerves on occasion, but once the tissues heal, the nerves also reapproximate around the mesh fiber. It is not possible to determine on the basis of morphology alone any related clinical symptoms. Furthermore, the presence of ganglia associated with these nerves indicates that the nerves are autonomic in nature and do not transmit pain sensation.

Figure Set 4. These figures depict normal nerves containing ganglion cells. The ganglion cells indicate the nerves associated with them are autonomic (not sensory). There is no histologic or pathologic evidence that the nerves or ganglia are affected by the mesh.

Figure 5. The figure depicts normal mucosa and normal submucosa with normal pattern of innervation. The mesh spaces/fibers at the bottom of the figure are associated with a normal and expected chronic inflammatory response.

Figure Set 6. These figures depict normal blood vessels that typically occur in vaginal submucosa. There is no indication that these blood vessels are dilated or congested. The areas that are designated as “edematous” or as “edema” are normal, loose fibroconnective tissue. In any event, the presence of mild edema, mild vascular congestion and mild vascular dilatation can be seen in the context of surgery and reflect a recent event – not a chronic process. “Fluid bubbles” is not a standard histologic or pathologic term.

Figure Set 7. This set of figures shows mesh material adjacent to skeletal (striated) muscle, adipose tissue, fibrous tissue, and nerves. Figures 7a and 7b are poor quality and it is not possible to determine at this magnification whether the striated muscle is scarred. In addition to having been modified by computer, the magnification is too low to evaluate the status of the muscle fibers. Striated muscle is normally present in this area and since the mesh is placed in an area that is weakened in pelvic organ prolapse, repair of this area using mesh explains these photos. There is no significant inflammation associated with the striated muscle to indicate an adverse effect. The presence of histologically normal nerves in this area indicates normal innervation and integration of the mesh and adjacent tissue. Figure 7c depicts muscle atrophy with intervening

fibrous tissue in absence of mesh material. The S-100 stain highlights the presence of nerve fibers while desmin appears to highlight muscle fibers. There is no evidence of nerve or muscle damage at this magnification. It is not clear what is meant by the term "mesh scar plate" in these figures as much of the area that is so designated appears to represent normal fibroconnective tissue.

Figure Set 8. – These figures show mesh spaces and fibers with the mild and expected foreign body giant cell reaction. Normal fibroconnective tissue is also present. The smooth muscle actin stains are difficult to interpret due to high background staining. There is no evidence of a pathologic effect on these tissues.

Figure Set 9. This figure set is particularly problematic in terms of interpretation. They appear to depict a small caliber blood vessel that has undergone partial obliteration, but there is no obvious thrombus and part of the vessel appears to be collapsed as opposed to occluded. The damage is likely secondary to surgery. There is no vasculitis. An EVG stain should be used to demonstrate vascular thrombosis and/or vessel wall damage. The "capillary thrombosis" in Figure 9b appears to represent fibrin and sludging as opposed to a true thrombus; it appears recent and likely secondary to surgical excision of the mesh.

Figure Set 10. These figures that purport to demonstrate curling and folding of the mesh material are fanciful at best. Some of the areas labeled as "scar" appear to be normal dense fibroconnective tissue containing normal vessels and nerves. The apparent "folding" and "curling" (macroscopically or microscopically) of mesh material after it has been excised does not provide information regarding the status of the mesh in vivo. This is especially true given the manipulation during surgical removal and subsequent sectioning and processing of the mesh explant. Dr. Iakovlev's computer altered yellow colorations are purely speculative. .

Figure Sets 11 and 12. These figures depict vaginal mucosal mesh erosion. Erosion is a well-known, but rare complication of a midurethral sling. The findings are expected and normal when erosion occurs. Bacterial colonization may occur – the vaginal mucosa is not sterile – but the figure is taken at too low of a magnification to identify bacterial colonies. Atrophy and mucosal erosion may occur in the vagina in postmenopausal women without mesh implants. These non-mesh erosions may also be associated with bacterial colonization.

Figure Sets 13-19. These figures purport to demonstrate polypropylene degradation that occurs in vivo. However, there is no reliable evidence that the "cracking" and "fragmentation" occurred in vivo and there is no evidence that if it did, it is of any clinical significance. In many areas purported to show degradation, there is no nearby inflammation.

Figure Set 20. The presence of dystrophic calcification may occur in a variety of settings, in the absence of prior surgery, as well as in absence of foreign material. In this case, the dystrophic calcifications are more likely a result of prior surgery. Scattered dystrophic calcifications are rarely, if ever, associated with adverse effects.

V. COMPENSATION

My hourly rate for work in this case is $500 per hour.

VI. REFERENCES

Woodruff AJ, et al. Histologic comparison of pubovaginal sling graft materials: a comparative study. Urology 2008; 72:85-89.

Huffaker RK, et al. Histologic response of porcine collagen-coated and uncoated polypropylene grafts in a rabbit vagina model. Am J Obstet Gynecol 2008; 198:582.e1-582.e7.

Boulanger L. Tissue integration and tolerance to meshes used in gynecologic surgery: an experimental study. Eur J Obstet Gynecol Reprod Biol 2006; 125: 103-108.

Boulanger L. Bacteriological analysis of meshes removed for complications after surgical management of urinary incontinence or pelvic organ prolapse. Int Urogynecol J 2008; 19:827- 831.

Engelsman AF. In vivo evaluation of bacterial infection involving morphologically different surgical meshes. Ann Surg 2010; 251:133-137.

Nilsson CG. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013; 24:1265- 9.

Serati M. Tension-free Vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urol 2012; 61: 939- 946.

Abbel-fattah M. Prospective randomised controlled trial of transobturator tapes in management of urodynamic stress incontinence in women: 3-year outcomes from the Evaluation of Transobturator Tapes Study. Eur Urol 2012: 62:843- 851.

Tincello DG. The TVT Worldwide Observational Registry for Long-Term Data. Safety and efficacy of suburethral sling insertion approaches for stress urinary incontinence in women. J Urol 2011; 186:2310- 2315.

Olsson I. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence. Int Urogynecol J 2010; 21:679- 683.

Cox A, et al. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013;10:78-89.

Ford AA, Ogah JA. Retropubic or transobturator mid-urethral slings for intrinsic sphincter deficiency-related stress urinary incontinence in women: a systematic review and meta-analysis. Int J Urogynecol. 2015 Jul 29. [Epub ahead of print]

Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014; 211:71.e1-71.e27.

Richter H. et al. Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med. 2010; 362:2066-76.

Falconer C. Influence of different sling materials on connective tissue metabolism in stress urinary incontinence. Int Urogynecol J 2001;12 (Suppl 2): S19-S23.

Elmer C. Histological inflammatory response to transvaginal polypropylene mesh for pelvic mesh reconstruction. J Urol 2009; 181: 1189-1195.

Hutchinson R. An exploratory 91-day tissue reaction study of polypropylene-based surgical mesh in rats (PSE ACC. No. 00-0035). July 2001.

Moalli PA. Tensile properties of five commonly used mid-urethral slings relative to the TVT. Int Urogynecol J 2008; 19: 655-663.

Lo TS, Horng SG, Liang CC, et al. Ultrasound assessment of mid-urethra tape at three-year follow-up after tension-free vaginal tape procedure. Urology 2004; 63:671-675.

Dietz HP, Mouritsen L, Ellis G, et al. Does the tension-free vaginal tape stay where you put it? Am J Obstet Gynecol 2003; 188:950-953.

Hill AJ, Unger CA, Soloman ER, et al. Histopathology of excised midurethral sling mesh. Int Urogynecol J 2015; 26:591-595.

Klosterhalfen B et al. Influence of implantation interval on the long-term biocompatibility of surgical mesh. Br J Surg. 2002; 89(8):1043-8.

AUGS/SUFU Position Statement, 2014.

Maher C, Feiner B, Baessller K, Christmann-Schmid C et al. Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse (Review). Cochrane Collaboration 2016.

Gad N, Duvvuru A, Burchgart B. Outcome of Prolift mesh repair in treatment of pelvic organ prolapse and its effect on lower urinary tract symptoms: 5-year retrospective case study. J. Obstet. Gynaecol. Res. 2013;39(1):243-9.

Jacquetin B, Hinoul P, Gauld J, Fatton B et al.. Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int. Urogynecol. J. 2013; 24:1679–1686.

Khan Z, Thomas L, Emory SJ. Outcomes and complications of trans-vaginal mesh repair using the Prolift kit for pelvic organ prolapse at 4 years median follow-up in a tertiary referral centre. Arch. Gynecol. Obstet. 2014; 290:1151-1157.

Bendavid R et al. A mechanism of mesh-related post-herniorrhaphy neuralgia. Hernia 2015; Nov 15 [Epub ahead of print].

Nieminen K et al. Outcomes after anterior vaginal wall repair with mesh: a randomized, controlled trial with a 3 year follow-up. Am. J. Obstet. Gynecol. 2010; 203:235.e1-8.

Withagen M et al. Trocar-guided mesh compared with conventional vaginal repair in recurrent prolapse. Obstet. & Gynecol. 2011; 117(2):242-250.

Dated: March 2, 2016

_____

Teri Longacre, MD